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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/225,426	01/05/1999	JOHN P.N. ROSAZZA	P00297US1	2480

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EXAMINER
SAUCIER, SANDRA E

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/225,426	ROSAZZA ET AL.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communicati n appears on th cover she t with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 17-19 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The claims are examined to the extent that they read on peptides as elected in paper # 9. As art has been applied on the elected embodiment □peptides□, search and art for other embodiments, such as L-arginine or polyarginine has not been applied since they are clearly not peptides. See MPEP 809.02 for examination with regard to election of species.

Claim Rejections - 35 USC § 112

Indefinite

Claims 1, 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Please note that L-Arginine is NOT A PEPTIDE, OLIGOPEPTIDE OR PROTEIN contrary to the grouping in claim 1. This makes the claim indefinite because the claim is not scientifically accurate and does not use the standard definitions in the art.

Scope of enablement

Claims 1, 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes and gastrointestinal disorder does not reasonably provide enablement for preventing any disorder whatsoever, nor the treatment of any and all cardiovascular, bronchial disorders or ischemic stroke or systemic hypotension, multiple sclerosis, Huntingon's, Parkinson's or Alzheimer's diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Amount of guidance and working examples

There are no working examples directed to the administration of any peptide in any cell culture or animal model of any disease. No prevention or treatment of any disease or disorder or condition is demonstrated.

Nature of the invention

The invention is directed to the prevention and treatment of any NO-mediated disease by the administration of claim specific peptides.

Nature of the prior art and unpredictability

Huntington's disease has no currently effective therapy according to peer reviewed article by Smith et al. published in 2003 [U1]. See abstract.

Parkinson's disease has only partially effective symptomatic treatments according to peer reviewed article by Trojanowski et al. [V1] published in 2002. See abstract.

Multiple sclerosis has no effective therapy according to peer-reviewed article by Van Noort [W1] published in 1996 and no effective treatments for primary progressive multiple sclerosis according to peer-reviewed article by Pender et al. [X1] published in 2002. See abstracts.

Alzheimer's disease has a treatment that only temporarily affords cognitive benefit. The treatment is characterized as only temporarily effective by McGeer et al. [U2] in a peer-reviewed article published in 2003. See abstract.

Further, administration of bradykinin to rats induces Alzheimer-like symptoms and is proposed as a model for Alzheimer's disease according to Wang et al. [V2].

Intravenous administration of bradykinin produces systemic hypotension. It is unclear how the administration of bradykinin is used to treat or prevent systemic hypotension or the full scope of "cardiovascular disorders" which includes systemic hypotension , when the prior art clearly indicates that IV administration of bradykinin produces systemic hypotension and aerosol administration has no cardiovascular effects. See Slocombe et al. [W2] or Riccioppo et al. [X2].

Bradykinin administration elicits bronchoconstriction according to Barnes [U3] or Polosa et al. [V3]. Further, according to Polosa et al. administration of Lys-BK or bradykinin produces a fall in expiratory volume in subjects with asthma. A decrease in expiratory volume is not an effective treatment for asthma which is a bronchial disorder. Polosa et al. also state that Des-Arg9 BK has no effect on expiratory volume, see abstract.

Bradykinin administration promotes neuronal tissue damage in brain ischemia according to Zausinger et al. [W3] published in a peer-reviewed article in 2002 (abstract). Therefore, this would not be a reasonable treatment for stroke.

Breadth of the claims

The invention is broadly claimed to prevent or treat any NO-mediated disease using the claim specific peptides which includes diseases for which no current effective treatment, much less any preventative treatment exists.

Undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

Pharmaceutical therapies in general are unpredictable for the following reasons: (1) therapeutic compositions may be inactivated before producing an effect, i.e. such as proteolytic degradation of the peptide or protein; (2) the therapeutic composition may not reach the target area, I. e. the peptide or protein may not be able to cross the mucosa or may be adsorbed by fluids, cells and tissues where the peptide or protein has no effect, (3) other functional properties, known or unknown, may make the therapeutic composition unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992).

Although the specification discloses methods of administration of the claim specific peptices in vitro, there are no data on the effectiveness of these peptides used in a therapeutic treatment of a particular disease. Therefore, in view of the nature of the invention, the state of the prior art, the amount of guidance present in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention.

Further, BK fragment 2-7 and Met-Lys-BK have no activity according to applicants' own specification.

Claim Rejections - 35 USC § 102

Claims 1, 17 and 19 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by US 4,585,757 [A].

The claims are directed to a one step method of administering a peptide, oligopeptide or protein containing an arginine available to NOS, to a mammal in order to regulate NO production for the prevention or treatment of certain NO mediated pathogenic conditions, wherein the peptide is L-

arginine, poly-arginine, BK, Des-Arg-1-BK, Des-Arg-9-BK, BK fragment 1-7, BK fragment 2-7, [Lys1]-BK, Lys-BK, Ile-Ser-BK, Met-Lys-BK.

(The claims are examined to the extent that they read on peptides, not L-arginine or polyarginine which are not peptides.)

US 4,585,757 discloses the administration of bradykinin in the range of 50-500 µg/kg to lower blood pressure (Table 2). The peptides are used to treat hypertension which is a cardiovascular disorder.

Response to Arguments

Applicants argument that the incorporation of the elements of claim 13 eliminate the rejection over '757 is not understood as administration of bradykinin to treat a cardiovascular disorder is claimed.

Claims 1, 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated over US 4,152,425 [B].

The claims have been discussed above.

US 4,152,425 discloses the infusion of 10-3000µg of kinin/l solution. The specifically preferred kinin is bradykinin. The infusion amount is exemplified at one liter (col. 5, l. 18). The treatment is for shocks from various causes such as post-surgical recovery, infections etc..

Response to Arguments

Applicants argue that the amount to be administered in the claim is a "therapeutically effective amount", and that this is distinct from the amount administered in '425.

This is not persuasive because the reference teaches the use of 10-3000 micrograms/liter of solution which can be calculated to be 3000µg/l/80kg = 37.5µg bradykinin/kg . This is within the range of administration of bradykinin taught in the specification at page 36.

Applicants argue that '425 co-administers glucose which would destroy the basic and novel characteristics of the claimed invention. While the reference of '425 does include the co-administration of glucose, applicants fail to demonstrate how the co-administration of glucose would destroy the characteristics of the invention.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz , 537 F.2d 549, 551 - 52, 190 USPQ 461, 463 (CCPA 1976)(emphasis in original)(Prior art hydraulic fluid required a dispersant which appellants argued was excluded from claims limited to a functional fluid "consisting essentially of" certain components. In finding the claims did not exclude the prior art dispersant, the court noted that appellants' specification indicated the claimed composition can contain any well - known additive such as a dispersant, and there was no evidence that the presence of a dispersant would materially affect the basic and novel characteristic of the claimed invention. The prior art composition had the same basic and novel characteristic (increased oxidation resistance) as well as additional enhanced detergent and dispersant characteristics.). See also Atlas Powder Co. v. E.I. duPont de Nemours & Co. , 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama - Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. v. Calco, Ltd ., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988).

When an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also Ex parte Hoffman, 12 USPQ2d 1061, 1063 - 64 (Bd. Pat. App. & Inter. 1989)("Although `consisting essentially of' is typically used and defined in the context of compositions of matter, we find nothing intrinsically wrong with the use of such language as a modifier of method steps . . . [rendering] the claim open only for the inclusion of steps which do not materially affect the basic and novel characteristics of the claimed method. To determine the steps included versus excluded the claim must be read in light of the specification . . . . [I]t is an applicant's burden to establish that a step practiced in a prior art method is excluded from his claims by `consisting essentially of' language.").

Applicant has not met this burden.

Claims 1, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Tobe et al.[X3].

Tobe et al. disclose the administration of bradykinin during ischemia and the improvement in electrical stability of the bradykinin-treated hearts.

Claims 1, 17-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Uehara et al.[U4].

Uehara et al. disclose the administration of bradykinin to diabetic mammals.

Claims 1, 17 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartl et al. [V4] or Palitzsch et al. [W4].

Hartyl et al. disclose the administration of bradykinin to patients with gastrointestinal condition.

Palitzsch et al. disclose the administration of bradykinin to rats to treat ethanol induced vascular injury.

Claims 1, 17-19 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,143,719 [A1].

US 6,143,719 disclose the administration of BK or Seq. ID #19 to rabbits (col. 20) to prevent platelet aggregation in coronary thrombosis and stroke (col. 6)

Claims 1 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by US 4,177,261 [B1].

US 4,177,261 disclose the administration of bradykinin or kallidin in order to promote the healing of wounds. Poor wound healing is one of the symptoms of diabetes.

Claim Rejections - 35 USC § 103

Claims 1, 17, 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chahine et al.[X4].

Chahine et al. disclose the administration of bradykinin or des-Arg9-bradykinin to ischemic hearts decreases fibrillation. Therefore it would be obvious to administer these peptides to a mammal during ischemia to prevent fibrillation.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1651. The supervisor for 1651 is M. Wityshyn, (703) 308-4743. The

normal work schedule for Examiner Saucier is 8:30AM to 5:00PM Monday and Tuesday and 8:30AM to noon on Wednesday.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (703) 308-1084. **Status inquiries must be directed to the Customer Service Desk at (703) 308-0197 or (703)-308-0198.** The number of the Fax Center for the faxing of papers is (703) 308-2742 or (703) 305-3592.

Sandra Saucier
Primary Examiner
Art Unit 1651
August 22, 2003